

Endometriosis

A Clinical and Pathological Study of 219 Cases

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SUMMARY

One hundred twenty-four cases of external endometriosis and 95 cases of adenomyosis were analyzed. The two are clinically different diseases which have one feature in common—a reactive fibrosis to aberrant endometrial tissue. They are coexistent in about the same frequency as would result from a non-causal relationship.

The origin of external endometriosis from the epithelial "inclusion" cyst is considered proven histologically. This is the source of origin of most external endometriosis, although occasional involvement from regurgitated endometrium probably occurs. Both the endometrial and the serous cysts have a common parentage in this anlage.

Certain histological features that are considered pathognomonic of endometriosis are: (1) the minimal lesion, (2) the characteristic cuboidal lined cyst, (3) the siderophagic cyst without lining, and (4) the siderophagic nest.

Recognition of the siderophagic nest will permit identification of extinct endometriosis and thus aid in studies to determine the spontaneous or therapeutically induced regression of the disease.

The coexistence of endometriosis with other pelvic pathological changes, notably carcinoma, indicates the need for further studies to search the possibility of relationship.

The ability of ectopic deposits of endometrium to become malignant on rare occasions would appear to be proven, but it is a rare occurrence and there is no justification for regarding endometriosis as a premalignant disease.

ENDOMETRIOSIS is a disease in which there are ectopic deposits of endometrial tissue in various parts of the body giving rise to obscure but fairly characteristic symptoms. Descriptions of this disease date back to closing years of the 19th century but Sampson^{7, 8, 9, 10} first recognized its fundamental nature, and his descriptions of its manifestations cannot be improved upon today. Whereas formerly knowledge of the disease was limited, today

knowledge of its existence is fairly widespread and the clinical diagnosis is made with increasing frequency. On many occasions, however, the disease is recognized only after examination of pathological material. It is, on the other hand, all too often true that whereas the disease is recognized by the surgeon its diagnosis escapes the pathologist, a situation which is the reverse of that which usually obtains. The purpose of this presentation is to emphasize some of the more obscure but equally pathognomonic histological features of the disease and thereby facilitate the pathological diagnosis.

INCIDENCE

There is considerable evidence accumulating that endometriosis is a disease of increasing incidence. It is one of the most common gynecological diseases. Fallon¹ stated that it was more common in females than acute appendicitis. Various observers have stated that it affects from 15 to 30 per cent of women. The authors' figures are in harmony with these.

This increase in incidence has been attributed to a more frequent diagnosis on the one hand and to an actual increase; Meigs^{4, 5} has championed the latter view. In the authors' experience the increased incidence seems to be an absolute one. Although supporting statistics cannot be cited, the authors are convinced that they are encountering the disease more frequently than was the case 15 years ago. Meigs⁵ has stated that the reason for this increase lies somehow in the changed social and economic conditions of our modern society which delay marriage until the third and even fourth decades and thereby inhibit fecundity.

Records of Mercy Hospital show a yearly increase in the number of recognized cases, from two in the year 1930 to 65 verified cases in the year 1947. Of 4,751 uteri removed and examined at the Mayo Clinic from the years 1923 to 1934, uterine endometriosis was found in 482 cases, or 10.1 per cent.³ Another way to estimate incidence is to study the frequency with which the disease is encountered in an extended series of pathological examinations (Table 1). In the material studied, endometriosis was the most common disease entity affecting the ovary. These studies probably do not indicate the exact incidence of the disease in the female population since it is representative of a selected series of patients with gynecological complaints. However, it is a surprising figure considering that it is based upon a consecutive series of cases in which the ovary was subjected to routine pathological examination. The figures do not take into account the incidence of endometrial deposits in the uterine wall. Adenomyomas or adenomyosis were found in approxi-

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TABLE 1.—*Analysis of Pathologic Change of the Ovary, August 1946 to April 1949, Mercy Hospital, San Diego, California*

	CASES
1. Endometriosis (cysts and focal).....	108
2. Involution changes, miscellaneous.....	144
3. Follicle cysts.....	88
4. Corpus lutein cysts.....	84
5. Salpingo-oophoritis.....	63
6. Serous cysts.....	53
7. Dermoid cysts.....	28
8. Pseudomucinous cysts.....	20
9. Fibroma.....	16
10. Papillary serous cystadenocarcinoma.....	15
11. Papillary serous cystadenoma.....	10
12. Theca-cell tumor.....	4
13. Krukenberg's tumor.....	4
14. Pseudomucinous cystadenocarcinoma.....	2
15. Brenner tumor.....	2
16. Granulosa-cell tumor.....	1
TOTAL.....	642
Percentage endometriosis.....	16.8%

TABLE 2.—*Pathological Findings in a Consecutive Series of 762 Uteri Examined in the Period August 1946 to April 1949*

	CASES
Fibromyomata.....	454
Fibrosis uteri, prolapse, normal or incidental to other pelvic pathology.....	144
Adenomyomas, adenomyosis.....	112
Peritoneal endometriosis.....	7
Carcinoma of endometrium.....	27
Carcinoma of cervix uteri.....	16
Sarcoma of uterus.....	2
TOTAL.....	762
Percentage adenomyosis.....	15.6%

TABLE 3.—*Analysis of 219 Cases of Combined External and Internal (Adenomyosis) Endometriosis*

External endometriosis (alone).....	113
External-internal endometriosis (coexistent).....	11
Internal (adenomyoma).....	95
TOTAL CASES.....	219

mately 15 per cent of uteri examined, and adenomyosis was about one-fourth as common as fibromyomas, as is shown in Table 2.

ENDOMETRIOSIS VERSUS ADENOMYOSIS

Endometriosis is sometimes described as existing in two forms, (1) external and (2) internal. The latter is synonymous with adenomyosis. In this condition, a direct continuity is said to exist between endometrium lining the uterus and aberrant endometrium in the uterine wall. As both are diseases of unknown cause, it is impossible to settle the question as to whether these are the same or two different diseases. In some cases external and internal endometriosis are coexistent, and the anatomical appearances indicate that, in these cases at least, the two are merely different manifestations of the same disease. The incidence of this coexistence is shown in Table 3.

The coexistence of external and internal endometriosis might thus be explained as purely fortuitous, and it certainly does not point to a common etiologic factor. On the other hand, it does not disprove a common causative factor, a point which will be discussed later.

PATHOLOGICAL ANATOMY OF ENDOMETRIOSIS

Wherever endometrium exists as a foreign tissue, it excites certain pathological tissue responses. These may be summarized as hemorrhage and reactive fibrosis. The sequelae of hemorrhage are, in turn, abnormal hemosiderin deposits, often with small focal calcifications. In the uterine wall, invading endometrium results in localized or diffuse fibrous thickenings with a characteristic trabeculation which is readily recognized. Not infrequently small bluish or chocolate-colored cysts, a few millimeters in diameter, are seen in the midst of the thickened areas of myometrium. In about 49.4 per cent of cases, fibromyomas and adenomyoses are associated in the same uterus. A frequent site of small solitary adenomyomas is in the region of the uterine cornu.

In the ovary, endometriosis exists in two forms, (1) as the endometrial cyst and (2) as the endometrial implant. The endometrial or chocolate cysts vary in size from 1 cm. to 20 cm. in diameter. They are bilateral in the vast majority of cases and almost invariably are ruptured during removal. The content varies from a fresh hemorrhagic liquid to a thick, chocolate-colored, tarry fluid. Although most such cysts are unilocular, some are multilocular. After the fluid is evacuated, the lining is often found to be roughened and dull, but it is sometimes smooth and chocolate-stained. The stain will not remove with washing. The focal endometrial implant is often a small blueberry spot, a few millimeters in diameter, indistinguishable from small hemorrhagic follicles unless associated with other unmistakable lesions. The implant undoubtedly represents an early stage of the cyst.

The pathological stigmata of the disease are well recognized by the astute surgeon. They should be searched for, whenever possible, in every laparotomy on female patients. Small or large, puckered adhesions in the cul-de-sac and the uterosacral ligaments accompanied by "blueberry spots" around the lower pelvic peritoneum are diagnostic of the disease. In the later stages, dense adherent peritoneal bands will be found over the posterior uterine surface, often uniting it to the sigmoid colon. In some cases this union may be indissoluble except by surgical resection of a portion of the sigmoid colon. Endometriosis thus causes a type of chronic chemical peritonitis.

Unfortunately when the pathological specimen reaches the pathologist, frequently distorted by fixation, the peritoneal manifestations are no longer recognizable. The authors have made it a routine practice to examine all roughened adhesions or hemorrhagic areas, particularly from the posterior uterine peritoneum and routinely from the cul-de-sac. As a result an increasing number of endometrial implants (Figure 3) are being discovered. Peritoneal

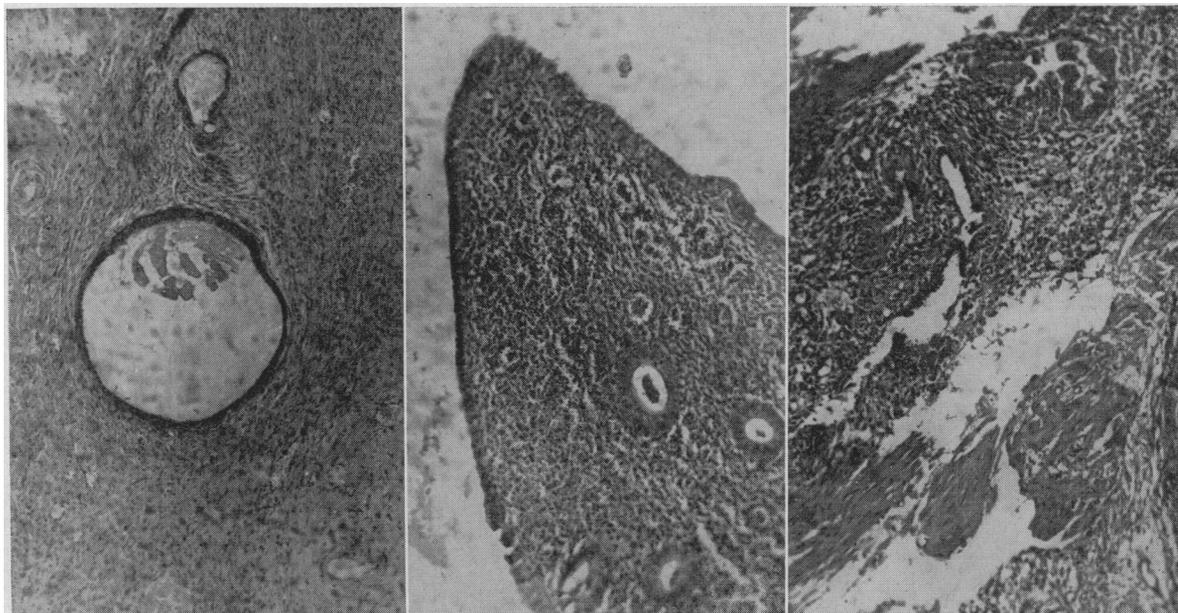


Figure 1

Figure 2

Figure 3

Figure 1.—Low-power photomicrograph of ovary, showing small endometrial implants. Endometrial stroma is beginning to appear about the smaller implant. This lesion is termed "minimal lesion" by the authors.

Figure 2.—A classical endometrial implant in an ovary (low power). Lesions of this type are readily recognized.

Figure 3.—An endometrial implant discovered in a routine section of the peritoneum of the uterine cul-de-sac (low power).

endometriosis is a creeping, migratory disease and spreads over the surface of the fallopian tubes, appendix, loops of small intestine and often up to the umbilicus. The anatomical sites in which the authors have discovered the disease are shown in Table 4.

However, the figures in Table 4 do not indicate the actual extent of peritoneal involvement of pelvic structures since they are based on pathological examinations and not upon surgical findings. Obviously, tissue from the pelvic peritoneum will not be available for examination in many instances in which endometriosis is involved. The rectosigmoid involvement is particularly understressed and probably occurs in some degree in about 25 per cent of cases.

PATHOGENESIS OF ENDOMETRIOSIS

Despite years of pathological and experimental investigation, the knowledge of the pathogenesis of endometriosis is considered to be theoretical. It would seem that insofar as it is possible to prove anything by means of morphological examination, the material already exists for determining the pathogenesis of endometriosis. The present theories of histogenesis may be summarized as (1) Sampson's theory of retrograde menstruation and implantation, and (2) the theory of celomic metaplasia. Adenomyosis is certainly a manifestation of endometrial implantation by direct extension. The authors are not in a position to deny that this mechanism may explain occasional cases of peritoneal endometriosis. In one case, bilateral hematosalpinx with endometrial-like tissue lining the fallopian tube was

observed. A fistulous tract extending from the uterus to the lower abdominal wall was observed in another case as a complication of cesarean hysterotomy. Hosai² has reported other examples of this complication. Morphological criteria indicate in a manner as convincing as possible that in the majority of instances endometriosis is the result of metaplasia of celomic mesothelium. It is the authors' belief that endometriosis and serous ovarian cysts have a common origin through a mechanism of celomic metaplasia and are both derived from the so-called epithelial "inclusion" cyst.

The mesothelium covering the adult ovary frequently appears as an epithelial-like border of low cuboidal cells and is identical with the lining of small glandular inclusions frequently encountered in routine histological examination of the ovary.

TABLE 4.—Anatomical Distribution of Lesions of Endometriosis in a Series of Combined "External" and "Internal" Endometriosis

SITES	CASES
Ovaries	107
Uterus	106
Cul-de-sac and posterior fornix.....	21
Fallopian tube.....	19
Cervix	8
Appendix	5
Sigmoid colon	4
Ileum	1
Omentum	1
Bladder	1
Hernia sac	1
Pelvic lymph node	1
TOTAL	275

Novak⁶ has termed these inclusions as "inclusion cysts." They may arise in a downgrowth of surface mesothelium or may be derived from ovarian mesenchyme. In any event, the authors are convinced that this is the precursor of the endometrial cyst; these typical "inclusion" cysts were found in most of the material associated with the unmistakable lesions of endometriosis, and the coexistence was too frequent to be casual or accidental. In cases of endometriosis of the ovary, these cysts frequently are found containing bluish staining mucoid content although the lining cells do not contain mucus. All "inclusion" cysts do not become endometrial cysts, but it is the authors' belief that in all or most cases ovarian endometriosis is preceded by the so-called inclusion cyst.

The determination of the direction in which the "inclusion" cyst will develop is dependent upon certain factors or influences, probably of a hormonal nature, which are unfortunately incompletely understood. This development may remain arrested and never progress beyond the "inclusion" stage. On the other hand, given the proper stimulus, it may develop either into the endometrial cyst or into the serous cyst, papillary serous cystadenoma or its malignant counterpart, the papillary serous cystadenocarcinoma.

This explanation, which is believed to be as susceptible to proof as is anything based upon morphological criteria, recognizes the multipotentiality of ovarian tissue. The ovarian stroma assumes the character of endometrial stroma and the lining cuboidal cells of the "inclusion" cyst develop the ability of endometrium to secrete and to bleed, and the transformation is complete. In virtually every case in which there is unmistakable endometriosis in the ovary, a careful search with multiple sections will reveal the modified "inclusion" cyst, usually containing a small amount of mucoid content (Figure 1).

In summary, the epithelial "inclusion" cyst is the earliest undifferentiated stage of ovarian endometriosis and, when it contains a small amount of mucoid secretion, represents the earliest recognizable lesion of endometriosis. For this entity the term "minimal lesion" is suggested.

THE PROGRESSION OF ENDOMETRIOSIS

In most cases, the ovary is the primary site of external endometriosis. It is the storehouse whence the disease may spread to involve contiguous structures. The tempo of endometriosis is undoubtedly an individual matter and is dependent upon hormonal or other relationships at present incompletely understood. There has been, in the authors' experience and in that reported by others, a small percentage of cases in which adjacent pelvic structures, notably the fallopian tubes, were affected without demonstrable ovarian involvement. Either the ovaries are not affected or the involvement is so slight as to be unrecognizable. No doubt the para-ovarian mesothelium shares with the ovary this property of celomic metaplasia, but in lesser degree.

MICROSCOPIC RECOGNITION OF ENDOMETRIOSIS

It may seem superfluous to devote any consideration to a subject presumably so thoroughly known as the microscopic recognition of endometriosis. It may be helpful, however, to discuss certain histological criteria which the authors believe to be as unmistakably pathognomonic of endometriosis as is the discovery of classical endometrial-like implants in aberrant locations. These criteria permit the identification of waning and extinct endometriosis and assist in studies on the progress and outcome of the disease.

Classical endometrial implants merit little discussion. They are found at or near the surface of the ovary or in the substance and present the characteristic appearance of endometrial tissue, with glands and stroma. Fresh hemorrhages are sometimes seen within the glands or within the stroma or both, and older hemorrhages are even more frequent. They are found in a variety of locations such as the surface of the fallopian tube, the peritoneum of the uterus, and the omentum (Figures 2 and 3). Although bleeding aberrant endometrium is a frequent finding, the cyclic secretory or premenstrual phases were seldom observed in the material studied by the authors, which gives rise to the belief that in many if not most cases the aberrant endometrium bleeds, but less often (if not rarely) menstruates.

The Typical Chocolate Cyst: All chocolate cysts are not endometrial but the vast majority are. Timidity in making the diagnosis may delay treatment for a disease whose progress is capable of therapeutic arrest. The "typical" chocolate cyst has a columnar or cuboidal border, beneath which there is a characteristic, sometimes modified, endometrial stroma (Figure 4). The border may occasionally appear pseudociliated. The stroma at times may be replaced by masses of siderophagic cells or cells containing lipochrome pigment (Figure 5). These are phagocytic cells probably derived from stromal mesenchyme. They appear large, oval, rounded or polygonal in shape. The pigment is sometimes coarsely granular and at other times foamy in character with a pale yellow-brown color. Such cysts are easy to recognize but are sometimes not diagnosed as endometrial if the stroma is modified or atypical. Sampson illustrated the lesions in beautiful colored drawings in some of his monographs.

The Non-Epithelialized Siderophagic Cyst: In many cases, the columnar epithelial lining is either absent or not discovered by routine examination. The situation is parallel to that which exists when the common pilonidal cyst is examined and no epithelium can be discovered. In either case, the destructive process, hemorrhage and infection respectively, have destroyed all evidences of an epithelial lining. Small and large cysts lined by several rows of siderophages are as truly endometrial in origin as are the characteristic implants and cysts (Figure 5).

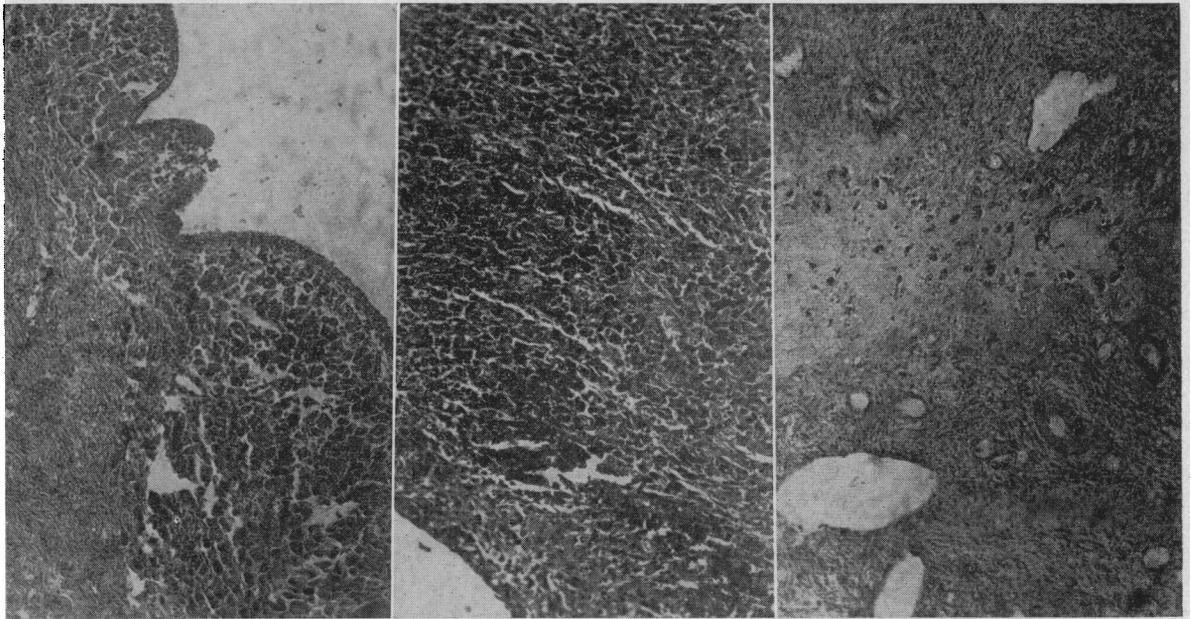


Figure 4

Figure 5

Figure 6

Figure 4.—Lining of a classical ovarian endometrial cyst (low power). The lining is formed of cuboidal or low columnar cells frequently with loosely arranged recognizable endometrial stroma cells. Note the collection of siderophages.

Figure 5.—Lining of an endometrial cyst formed of dense sheets of siderophages (low power). All trace of classical glands and stroma has been destroyed. Such cysts are frequently not diagnosed by the pathologist.

Figure 6.—The siderophagic nest (low power). This lesion is considered pathognomonic of extinct endometriosis.

The Siderophagic Nest: The authors use the term "siderophagic nest" to describe an ovarian lesion which as a stigma of endometriosis is considered as specific as the presence of the classical implant. (It was only hesitantly and after a review of the ovarian material studied that the conviction as to its pathognomoncity was reached.) The "siderophagic nest" is a small or large collection of siderophages found in the center of a fibrotic follicle. The authors believe it is an atretic follicle but cannot deny it may represent a luteinized follicle. It is seen regularly in ovaries that elsewhere show unmistakable implants or cysts. If such a lesion is present in an ovary in which there is no characteristic implant, extinct endometriosis is indicated, which is important in studying the stages of the disease.

Skeptics may question this report of the lesion, perhaps attributing it to over-enthusiasm. Therefore it should be noted that hemorrhage of the corpus luteum rarely leaves blood pigment; the hemorrhage is single and unrepeatd and the site is spontaneously and completely repaired. Endometrial hemorrhages, on the other hand, are repeated and result in a reactive fibrosis whereby the hemorrhagic fluid becomes entrapped (Figure 6). It persists for long periods, probably years. The "siderophagic nest" thus formed may occasionally calcify and, rarely, produce bone in the ovary. An ossified fibrous ovary may result from endometriosis, as was indicated by findings in one of the cases studied.

Clinical Features: Clinical descriptions of the disease leave little that can be added. In the series studied by the authors, the average age of patients with external endometriosis was 37.3 years. The

youngest patient was 21 years of age and the oldest 55. The duration of symptoms varied from one month to eight years, with the average 1.6 years. The commonest symptoms were progressive secondary dysmenorrhea, pelvic pain, menorrhagia, dyspareunia and infertility. Infertility was a common symptom. Of 61 married patients, 21 had never been pregnant, 15 had been pregnant once, 17 twice, seven three times, and one eight times. The average number of pregnancies for the series in married females was 1.7.

Clinically, adenomyosis is a different disease (Table 5). The symptoms affect an older age group. The commonest symptom is irregular menopausal or post-menopausal bleeding. Examination of curetted material is frequently negative or shows a fixed proliferative endometrium.

ENDOMETRIOSIS IN SPECIAL LOCATIONS

1. *Endometriosis of the Para-umbilical Region:* Endometriosis of the anterior abdominal wall in or about the umbilicus is always a manifestation of external endometriosis. Novak⁶ cites about 60 recorded

TABLE 5.—*Contrasting Clinical Features of External Endometriosis and Adenomyosis*

	External Endometriosis	Adenomyosis
Average age	37.3 years	47.8 years
Duration of symptoms.....	21.9 months	12.6 months
Average number of pregnancies....	1.7	3
Predominant symptoms....	(1) Pelvic pain (2) Dysmenorrhea (3) Menorrhagia	(1) Irregular bleeding

cases. The present series contained four examples or about 3.5 per cent. In the four cases, two of the patients had had previous hysterotomy and cesarean section, one had not, and in one case the history was vague. In three cases, the endometrioma became swollen with the menses and in one case it did not. Umbilical endometriosis is cited as proof both of the implantation theory and of the theory of celomic metaplasia.

2. *Endometriosis of the Sigmoid Colon:* Involvement of the peritoneum of the sigmoid colon is present in many late cases. It indicates advanced disease. The involvement is commonly extrinsic. Operative description suggests an involvement in about 25 per cent of cases. Intrinsic endometriosis producing an infiltrating neoplastic-like lesion is rarer and probably exists in not more than 2 per cent of cases. In the authors' series, diagnosis of carcinoma was made in one case in which there was bleeding from the rectum. Similar errors had been made frequently before.

3. *Endometriosis of the Small Intestine:* One case of endometriosis in the terminal ileum occurred in the authors' series. The symptoms were those of "chronic" appendicitis. A small infiltrating tumor about 3 x 1 cm. involved the wall of the terminal ileum. "Chocolate cysts" were also present in the ovary.

4. *Endometriosis of the Appendix:* In the present series the peritoneum of the appendix was involved in only five cases (2.3 per cent), but it is probable that this is less than the usual incidence. The serosa presented a dull surface covered by fibrin-like deposits. Symptoms simulated those of appendicitis. This involvement is always secondary to right-sided ovarian endometriosis.

5. *Endometriosis of the Bladder:* Invasion of the bladder wall with tumor-like endometrial tissue is a rare occurrence. It occurred in one case in the present series, in a patient 27 years of age. In this case symptoms of bleeding and dysuria of six years' duration were so severe as to necessitate partial cystectomy. Extensive invasion was found. Diagnosis was made by biopsy of a suspicious lesion. The pre-operative diagnosis was made on the basis of history characteristic of endometriosis plus the fact that blood cells were found in a urine specimen taken by catheter at the time of menstruation. Associated limited ovarian involvement also was found.

6. *Endometriosis in Pelvic Lymph Nodes:* Endometrium has rarely been reported in pelvic retroperitoneal lymph nodes. The authors encountered it once in examination of material removed in a radical panhysterectomy with lymphadenectomy for carcinoma of the cervix.

7. *Endometriosis of the Cervix:* Endometriosis was encountered in the cervix in eight cases. In three of these it was found in routine biopsy of the cervix for other disease. In the remainder it was probably a manifestation of adenomyosis.

8. *Endometriosis and Carcinoma:* In 124 cases of external endometriosis, three malignant tumors

TABLE 6.—Associated Significant Pathological Entities in 124 Cases of External Endometriosis

	CASES
Endometriosis and adenomyosis.....	11
Endometriosis and salpingitis.....	12
Endometriosis and fibromyomata uteri.....	38
Endometriosis and endometrial cancer.....	2
Endometriosis and ovarian cancer.....	1
Endometriosis and other ovarian cysts or tumors.....	9
Endometriosis without significant associated diseases.....	51
TOTAL	124

were found—two adenocarcinomas of the endometrium and one papillary adenocarcinoma of the ovary. An unusual adenocarcinoma of the urinary bladder and pelvis in a 55-year-old patient who had had a previous hysterectomy bore some resemblance to a carcinoma of endometrial origin. These figures are not conclusive of any causal association, but warrant further study. The authors encountered one endometrial adenocarcinoma in a female 52 years of age. It arose in the right ovary and was associated with chocolate cysts. The uterus was small and free of cancer. Snyder¹¹ reported another case. The ability of ectopic endometrium to become malignant on occasion would appear to be proven. It is a rare occurrence, however, and under no circumstances is there warranty for regarding endometriosis as a "precancerous" disease.

9. *Endometriosis and Other Pelvic Disease:* Other pathological conditions found in the 124 cases of external endometriosis are shown in Table 6. The significance of the association cannot be determined at this time. If, however, infertility is a cause as well as a result of endometriosis, it seems logical that the incidence of other pelvic diseases should be higher among women who have endometriosis than among those who do not.

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